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On 2-25-04

TOWNSEND and TOWNSEND and CREW LLP

By: Karen Karlin

PATENT
Attorney Docket No.: 080309-000000US
Client Ref. No.: P10295-DrB/la

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

HORST LINDHOFER et al.

Application No.: 09/094,921

Filed: June 15, 1998

For: METHOD FOR EX VIVO IMMUNIZATION USING HETEROLOGOUS INTACT BISPECIFIC AND/OR TRISPECIFIC ANTIBODIES

Customer No.: 20350

Confirmation No. 9008

Examiner: Holleran, Anne L.

Art Unit: 1642

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. HORST LINDHOFER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, HORST LINDHOFER, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I received Ph.D. in the field of biology from Ludwig-Maximilians-University (LMU) in 1993. Currently I am CSO at TRION Pharma GmbH. I have been at this position and related positions for 6 years.

3. The present invention provides for the first time methods for obtaining an anti-tumor immunity in a patient by immunizing the patient with an antibody-tumor cell preparation that comprises bispecific antibodies capable of bringing tumor cells, T cells, and Fc receptor-bearing effector cells into close proximity. Certain isotype combinations are disclosed for making the bispecific antibodies of the present invention.

4. I am a named inventor on the above-referenced patent application. I am also the first author of the Lindhofer *et al.* reference (*J. Immunol.*, **155**:219-225, 1995). I have read and am familiar with the contents of this patent application. In addition, I have read the Office Action, mailed August 26, 2003, received in the present case. It is my understanding that the Examiner believes that the claimed invention is obvious over the references by Volker *et al.*, Deo *et al.*, and Lindhofer *et al.*, in part because the bispecific antibody isotype combination of rat/mouse is disclosed by the Lindhofer *et al.* reference.

5. This declaration is provided to demonstrate that, if one uses bispecific antibodies of the isotype combinations disclosed by Lindhofer *et al.* to prepare the antibody-tumor cell preparation of the present invention, there is no reasonable expectation of success in inducing an anti-tumor immunity.

6. It is well known in the field of immunology that antibodies are divided into several isotypes. For example, human antibodies belong to five isotypes: IgA, IgD, IgE, IgG, and IgM. Rat and mouse antibodies have the same general isotypes. These isotypes are further divided into subclasses. The mouse IgG isotype, for instance, consists of the subclasses of IgG1, IgG2a, IgG2b, and IgG3. Each isotype or subclass has distinct physiochemical characteristics and therefore a distinct Fc portion.

7. Even though the V regions of antibodies are responsible for antigen specificity, many functions of antibodies are mediated by their Fc portions via interaction with effector immune cells that bear Fc receptors on the cells surface. Antibodies of different isotypes or subclasses thus can mediate the action of different accessory cells, according to the type of Fc receptor expressed on the accessory cell surface. For example, at least three distinct types of Fcγ receptors have been identified, each with different affinity and selectivity for different IgG subclasses.

8. The present inventors have discovered that a bispecific antibody of an appropriate isotype or subclass combination is necessary for the successful practice of the present invention, because only bispecific antibodies of certain isotype/subclass combinations can recruit appropriate accessory cells that are necessary for anti-tumor immunity. When in close proximity to each other, such as when brought together to a tumor cell by a bispecific antibody of the present invention, a T cell and an accessory cell bearing Fcγ receptor type I or III which is able to phagocytose tend to achieve costimulation from crosstalk between cell surface molecules of the two cell types. On the other hand, Fcγ receptor type II (also known as CD32) is capable of delivering inhibitory signals and is present on e.g. B cells which are unable to phagocytose. Therefore, the recruitment of a T cell and a Fcγ receptor type II-bearing cell (as e.g. a B cell which is unable to phagocytose) to a tumor cell by a bispecific antibody of a different isotype/subclass combination may not lead to costimulation of the T cell and the Fc receptor-positive cells, and consequently, will not lead to a desired anti-tumor immunity.

9. If one uses a bispecific antibody of a particular isotype/subclass combination to elicit an anti-tumor immunity according to the present invention, the chance of success cannot be predicted before the antibody is actually made and tested for its efficacy. The Lindhofer *et al.* reference describes bispecific antibodies of the isotype combinations of rat-IgG2b/mouse-IgG2a and rat-IgG2a/mouse-IgG2a without offering any distinction between the two for their usefulness in practicing the method of the present invention. Only through our experiments we were able to determine that rat-IgG2b/mouse-IgG2a is a suitable isotype

combination, whereas a rat-IgG2a/mouse-IgG2a bispecific antibody is not effective for immunizing a patient against tumor cells.

10. In summary, even if one were to combine the teaching of the Volker, Deo, and Lindhofer references, there would be not reasonable expectation of success due to the diversity in the types of Fc receptors and the physiological functions of cells expressing the Fc receptors.

Date: 28.1.04 By: Horst Lindhofer

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